AAPS PharmSciTech (2020) 21:93
DOI: 10.1208/s12249-020-1628-0

Check for updates

Research Article

Exploring the Potential of Hydrophilic Matrix Combined with Insoluble Film Coating: Preparation and Evaluation of Ambroxol Hydrochloride Extended Release Tablets

Manyu Hu,[1,2,4] Zhuangzhi Zhu,[3] Yubo Wu,[2] Qingqing Meng,[2] Jing Luo,[3] and Hao Wang[2,3,4]

Received 19 September 2019; accepted 22 January 2020

Abstract. To explore the potential utility of combination of hydrophilic matrix with membrane-controlled technology, the present study prepared tablets of a water-soluble model drug (ambroxol hydrochloride), through process of direct compression and spray coating. Single-factor experiments were accomplished to optimize the formulation. *In vivo* pharmacokinetics was then performed to evaluate the necessity and feasibility of further development of this simple process and low-cost approach. Various release rates could be easily obtained by adjusting the viscosity and amount of hypromellose, pore-former ratios in coating dispersions and coating weight gains. Dissolution profiles of coated tablets displayed initial delay, followed by near zero-order kinetics. The pharmacokinetic study of different formulations showed that lag time became longer as the permeability of coating membrane decreased, which was consistent with the *in vitro* drug release trend. Besides, *in vitro*/*in vivo* correlation study indicated that coated tablets exhibited a good correlation between *in vitro* release and *in vivo* absorption. The results, therefore, demonstrated that barrier-membrane-coated matrix formulations were extremely promising for further application in industrialization and commercialization.

KEY WORDS: zero-order release; hydrophilic matrix tablets; membrane-controlled; hypromellose; ethylcellulose coating.

INTRODUCTION

The application of hydrophilic matrix technology as a drug delivery platform for oral extended release (ER) systems is quite common. Hypromellose (hydroxypropyl methylcellulose, HPMC) is widely used as the drug release rate-controlling polymer, due to its physicochemical characteristics such as high swellability and nonirritant, as well as global acceptance and availability (1). Some incontrovertible advantages of its usage include its pH-independent performance, cost effectiveness, also the simplicity of tablet formulation (2). In addition, it has the ability to provide a wide range of desired drug release profiles with high reproducibility (3,4). HPMC displays good compression performance. The preparation of hydrophilic matrix tablets can be accomplished by directly compressing a dry mixture of API, HPMC, and other excipients, which would avoid the drawbacks of wet granulation such as inapplicable to wet-sensitive drugs (3,5,6). However, due to drug molecules available at and adjacent to all the tablet surfaces dissolving immediately before complete gel layer formation, HPMC matrices containing a highly water-soluble drug often exhibit an initial burst at the beginning of drug release, which may result in undesired drug plasma levels and unexpected side effects (3,7,8). Moreover, the release rate of drug always decreases with time, often exhibiting first-order or near first-order kinetics.

Sometimes, simple modifications such as the application of various coatings could be considered to get more robust formulations. Polymeric film coatings also offer a great development potential for oral ER drug delivery (9–11). Water-insoluble polymers, such as ethylcellulose (EC), are often used as the main barrier-membrane (BM) materials. EC is popularly applied because of its non-toxic and non-irritable, good stability, great properties of film forming (12–14). Surelease® is one kind of commercially available aqueous EC dispersions (15). It is supplied as a 25% (*w*/*w*) solids dispersion containing dibutyl sebacate or glycerol tricaprylate/caprate as plasticizers, ammonium oleate as stabilizer, and other excipients. Aqueous polymer dispersions

[1] Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, 310014, China.
[2] National Pharmaceutical Engineering and Research Center, China State Institute of Pharmaceutical Industry, Shanghai, 201203, China.
[3] Shanghai Whittlong Pharmaceutical Institute, Shanghai, 201203, China.
[4] To whom correspondence should be addressed. (e–mail: humanyu951210@163.com; wanghao99@hotmail.com)

aaps

Published online: 19 February 2020

have some advantages, for instance, escaping the usage of organic solvents, higher solid content of coating formulations on account of low viscosity (16). However, tablets coated with a pure insoluble polymer usually show up with too slow or incomplete release (17). Therefore, permeability enhancers, which are hydrophilic, need to be added into film-coating formulations to modify drug release profiles (18). Pore-formers could be HPMC, hydroxypropyl cellulose (HPC), polyethylene glycols (PEG), *etc.* (14). Hydrophilic matrix combined with functional water-soluble film coatings could inhibit initial burst effect of highly water-soluble drugs. At the same time, it could increase the robustness of drug release and modify release profiles towards zero-order release. Compared with the more involved preparation of bilayer tablets and oral osmotic systems (OROS), the steps to prepare this dosage form are much simpler. Furthermore, OROS are normally coated with organic solvents which have environmental and toxicological concerns, as well as cost-related issues (19,20). Hence, the approach of combination might be a possible alternative to them. Recently, the release behaviors of uncoated and BM-coated hydrophilic matrices were compared, with hydrochlorothiazide as the model drug (21). The results showed that aqueous EC-coated matrices had minimal susceptibility to changed dissolution conditions and storage conditions. Simultaneously, drug release with near zero-order kinetics *in vitro* was realized. Afterwards, the robustness of *in vitro* drug release from EC-coated hydrophilic matrix tablets of metoprolol tartrate, a model drug of BCS class I, was investigated by simulating the physicochemical properties of gastrointestinal (GI) fluids and mechanical stress in human GI tract (22). The *in vitro* drug release at variable conditions was found to be consistent. However, there was no *in vivo* research, which was more meaningful. To further research the utility of this approach, the objective of the present study was to prepare BM-coated hydrophilic matrix tablets of ambroxol hydrochloride (AH) as the model drug, through process of direct compression and spray coating. Then, formulations were adjusted to flexibly obtain different release rates within effective range. Finally, *in vivo* pharmacokinetics of self-made tablets was performed in beagle dogs to explore the necessity and feasibility of further development of this simple process and low-cost approach.

MATERIALS AND METHODS

Materials

AH was purchased from Wuhan Yuancheng Technology development Co., Ltd. (Hubei, China). HPMC (METHOCEL™ K100LV/K4M Premium DC2 and K15M Premium CR), Surelease® (ethylcellulose aqueous dispersion, E-7-19020), and Opadry® (HPMC, OY-29020) were provided by Shanghai Colorcon Co., Ltd. (Shanghai, China). Mannitol (PEARLITOL® 200 SD) was obtained from Shanghai InnoPolymer Pharmaceutical Tech.Co., Ltd. (Shanghai, China). Microcrystalline Celluose (MCC; Avicel® PH102) and colloidal silicon dioxide (Aerosil® 200 Pharma) were bought from Shanghai Fenghong Pharmaceutical Excipients Tech. Co., Ltd. (Shanghai, China). Magnesium stearate (Hyqual®) was procured from Shanghai Chineway Pharmaceutical Tech. Co., Ltd. (Shanghai, China). Other chemicals were of analytical grade.

Preparation of Hydrophilic Matrix Core Tablets

The composition of core tablets is shown in Table I. The tablet weight was 300 mg with dose level of 75 mg. AH, HPMC, fillers, and colloidal silicon dioxide were sieved through a 40-mesh screen after accurately weighed and subsequently mixed for 15 min by a three-dimensional blender (WAB Machinery Co., Ltd., Shenzhen, China). The powder blends were then lubricated with magnesium stearate for 3 min and directly compressed into 8.8-mm standard biconvex round tablets by a single punch press (Beijing Gylongli Sci. & Tech. Co., Ltd., Beijing, China). Tablets were accurately weighed by an electronic balance (BSA223S-CW, Sartorius, Germany). Hardness for each formulation was measured by hardness tester (YD-35, Tianda Tianfa Technology Co., Ltd., Tianjin, China) ($n = 6$). Friability was determined by friabilator (FAB-2, Tianda Tianfa Technology Co., Ltd., Tianjin, China) with 22 tablets rolling at 25 rpm for 4 min ($n = 3$).

Coating of Core Tablets

Matrix tablets were coated with an aqueous dispersion system containing Surelease® and Opadry® in a solid content of 10% (*w/w*). To change the permeability of the EC barrier-membrane, different amounts of Opadry® were added to the film coating system. The ratios of Surelease® and Opadry® could be 80:20, 70:30, and 60:40 (*w/w*). The coating solution was prepared according to instruction before sprayed into core tablets to achieve a weight gain (WG) of 3–8% (*w/w*). The tablets were coated in a fully perforated coating pan (LABCOAT I, O'Hara Technologies, Canada) using a 0.8-mm nozzle, with coating parameters given in Table II. After coating, tablets were cured at 60°C for 6 h in an oven. The entire preparation process of the tablets is shown in Fig. 1.

Scanning Electron Microscopy

The coated tablets were cut by blade. Samples were coated with gold film under vacuum using a sputter coater (Emitech k550x, Quorum Technologies Ltd., Ashford, UK). The cross sections were then observed under scanning electron microscopy (SEM) (Quanta FEG, FEI, USA) at an acceleration voltage of 15 kV at a magnification of × 300.

In Vitro Release Study

USP Apparatus II

AH release from tablets were measured using USP apparatus II (paddles) (Agilent Technologies, Cary, USA) with sinkers in 900 mL dissolution media at 37°C ± 0.5°C. Because AH is absorbed in the intestine, the main release media was simulated intestinal fluid, phosphate buffer with pH 6.8. At a constant rotation speed of 50 rpm, samples were extracted at every predetermined time interval through a 0.45-μm Teflon filter and subsequently detected by a UV/Vis spectrophotometry (UV-2600, Shimadzu, Kyoto, Japan) at

Table I. The Composition of AH Core Matrix Tablets

Ingredients	Effect	Composition (% *w/w*)
AH	API	25.0
HPMC (METHOCEL™ K100LV/K4M Premium DC2/K15 M Premium CR)	Matrix material	25.0–50.0
MCC (Avicel® PH102)	Filler	10.0
Mannitol (PEARLITOL® 200 SD)	Filler	39.0–14.0
Colloidal silicon dioxide (AEROSIL®200 Pharma)	Glidant	0.5
Magnesium stearate (Hyqual®)	Lubricant	0.5
Total	–	100.0

the wavelength of 244 nm to determine drug contents. All experiments were performed at least in triplicate.

USP Apparatus III

To be answerable for the variability of pH through the GI tract, dissolution testing was also performed using USP apparatus III, reciprocating cylinder (BIO-DIS, Agilent Technologies, Cary, USA). The pH gradients and other experimental conditions of fasted state and fed state are described in the Table III (23–25). The preparation methods of dissolution media are shown in the Table IV. All samples were analyzed by a UV/Vis spectrophotometry at the wavelength of 307 nm. All experiments were performed at least in triplicate.

In Vivo Pharmacokinetic Study in Beagle Dogs

All the animal experiments were carried out in accordance with the guidelines of the National Act on the Use of Experimental Animals and were approved by China State Institute of Pharmaceutical Industry (SCXK 2017-0007).

Six healthy beagle dogs with the weight at 9.0 ± 1.5 kg were divided into two groups randomly. The dogs were fasted for 12 h and had free access to water before administration of self-made AH tablets with 40-mLwater. About 1.0-mL blood samples were withdrawn from foreleg vein of dogs at predetermined time points and transferred into heparinized centrifuge tubes immediately. The supernatant plasma samples were collected and then stored at −20°C after the centrifugation (Eppendorf 5424R, Germany) at 2500 rpm for 10 min.

An aliquot of 100 μL plasma sample, 10 μL internal standard solution (10 ng/mL diphenhydramine solution), and 400 μL protein precipitant (methanol: acetonitrile, 1:1, *v/v*) were added in a 1.5-mL plastic centrifuge tube and vortex-mixed (MIX-3000, Miulab, Hangzhou, China) at 3000 rpm for 3 min, followed by centrifugation at 13,000 rpm for 5 min. The supernatant was diluted at 1:1 ratio and then transferred to an auto-sampler vial for analysis. The plasma concentrations of AH were determined by LC-MS/MS (LCMS-8030, Shimadzu, Kyoto, Japan) using a Acquity UPLC® BEH C18 (100 mm × 2.1 mm, 1.7 μm, Waters, USA) column.

Table II. Parameters of Coating Procedure

Parameter	Value
Total tablets weight	250 g
Inlet temperature	56–58°C
Exhaust temperature	40–43°C
Bed temperature	39–42°C
Air flow velocity	80 m^3/h
Atomization pressure	1.2 bar
Spray rate	1.4–1.6 g/min
Pan speed	9 rpm

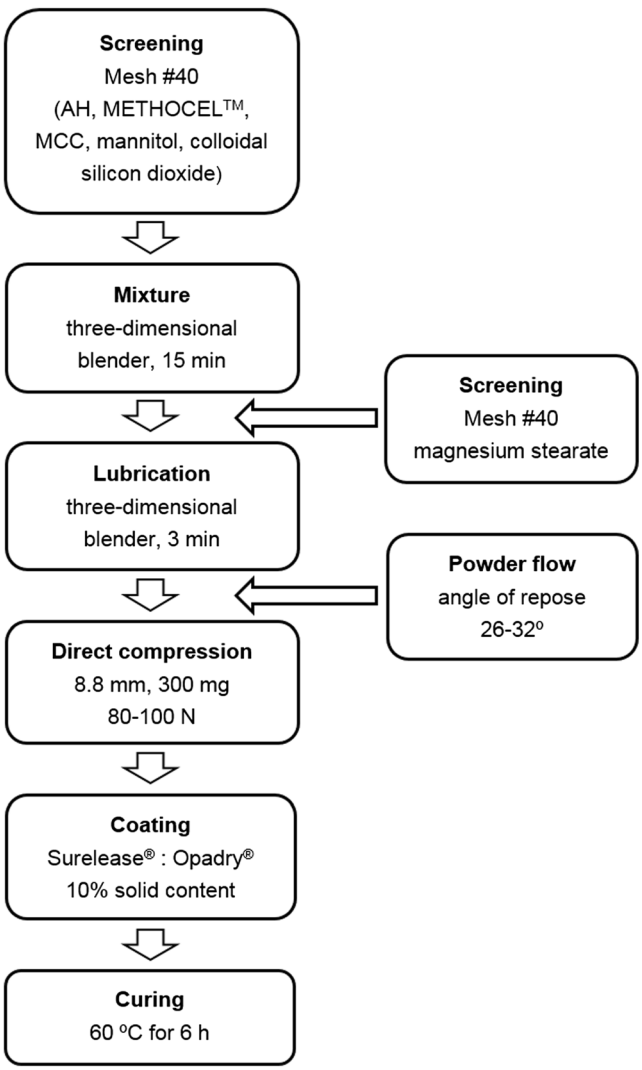

Fig. 1. Preparation process flow chart of AH coated tablets

Table III. Dissolution Media and Transit Times Used in Fasted and Fed Gradients

	Fasted state		Fed state	
GI segment	Media	Residence Times (min)	Media	Residence Times (min)
Stomach	FaSSGF pH 1.8	60	FeSSGF pH 5.0	120
Duodenum/proximal jejunum	Blank FaSSIF pH 6.5	60	Blank FeSSIF pH 5.8	60
Distal jejunum/proximal ileum	Blank FaSSIF pH 6.8	240	Blank FeSSIF pH 6.8	300
Distal ileum	Blank FaSSIF pH 7.2/7.5	300	Blank FeSSIF pH 7.2/7.5	240
Proximal colon	SCoF pH 5.8	300	SCoF pH 5.8	240
colon	Blank FaSSIF pH 6.8 Volume 250 mL	480	Blank FeSSIF pH 6.8	480
Settings	Top/bottom mesh 40 mesh/405 μm Dip rate 10 dpm		Bath temp 37.1 °C	

RESULTS AND DISCUSSION

In this study, robust AH matrix with unbroken, smooth film coats were successfully prepared. Core tablets and coated tablets were white color. The weight variation and content uniformity of tablets was up to standard. Friability of all formulations was less than 1%. The partial cross section of the coated tablets under scanning electron microscopy is shown in Fig. 2. The images showed that the coating film uniformly wrapped around the surface of the core tablets.

An illustration of the forms of AH coated tablets changed with time during release process is displayed in Fig. 3. Matrix swelled due to water permeation and expanded mainly in the axial direction, followed by rupture of barrier-membrane at the band of the tablets (21,26). Afterwards, matrix further expanded in the axial direction and drug released preferentially from the side face.

In Vitro Drug Release Studies

Effect of Viscosity and Amount of HPMC

With the rest of the formulation composition unchanged, drug release from uncoated AH matrix tablets with different viscosity grades of HPMC are illustrated in Fig. 4a. The 30% (*w/w*) amount of HPMC K100LV, K4M and K15M was used as extended-release agents respectively. As expected, K15M matrices produced the lowest drug release rate compared to K100LV and K4M (27). Overall, drug release was in the order of K100LV > K4M > K15M. Besides, K15M matrices were the most robust, as illustrated by the lowest value of standard error. As the viscosity of HPMC increased, the hydration rate got faster, the degree of swelling and the strength of the gel layer increased. Thus, the rate of drug through the gel layer slowed down. The results were consistent with the theories. HPMC matrices with higher viscosity were less susceptible to erosion as they had better inherent water-holding capacity (28).

On the other hand, due to its moderate release rate, HPMC K4M was selected as a representative to evaluate the effect of various HPMC amounts (25%, 30%, 40%,50%, *w/w*). As shown in Fig. 4b, the increasing amount of K4M reduced the release rate of core tablets. Higher content of HPMC made tablets hydrated faster and then rapidly formed thicker gel layer, which blocked drug release. The release rate in the early stage (0–8 h) was faster than that in the late stage (8–20 h) for all four prescriptions. The drug was quickly dissolved as the consequence of water penetration into the

Table IV. The Preparation Methods of Dissolution Media

Media	Preparation
FaSSGF pH 1.8	Mix 250.0 mL of 0.2 M sodium chloride and 102 mL of 0.2 M hydrochloric acid and dilute to 1000.0 mL with water
FeSSGF pH 5.0	Dissolve 4.65 g of sodium acetate in water, add 8.0 mL of 2 M acetic acid, and dilute to 1000.0 mL with water
Blank FaSSIF/FeSSIF pH 6.5/6.8/7.2	Mix 250.0 mL of 0.2 M potassium dihydrogen phosphate and 68.0/112.0/173.5 mL of 0.2 M sodium hydroxide and dilute to 1000.0 mL with water
SCoF pH 5.8	Mix 250.0 mL of 0.2 M potassium dihydrogen phosphate and 18.0 mL of 0.2 M sodium hydroxide and dilute to 1000.0 mL with water

FaSSGF fasted state simulating gastric fluid, *FeSSGF* fed state simulating gastric fluid, *Blank FaSSIF* fasted state simulating gastric fluid without bile compounds, *Blank FeSSIF* fed state simulating gastric fluid without bile compounds, *SCoF* simulating colon fluid

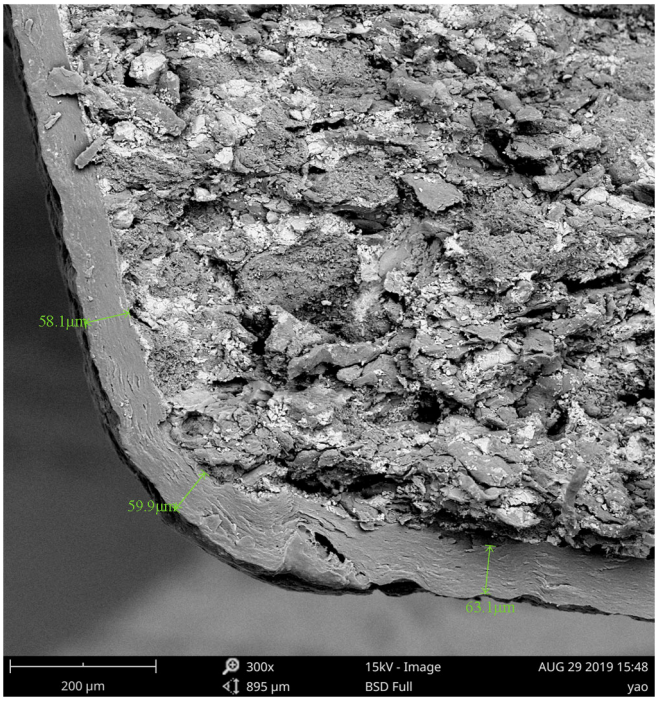

Fig. 2. A partial cross section of an AH coated tablet (Surelease®:Opadry®, 80:20, 5.5 ± 0.3% WG, *w/w*, × 300 magnification)

dosage form, and the drug molecules were not replaced, leading to decrease of drug concentration inside and thus the release rate decreased with time (4).

Effect of Tablet Hardness

The influence of the hardness of the HPMC K4M-based core tablets on drug release was also investigated. According to the results shown in Fig. 4c, there was no evident discrepancy among the three different hardness levels. In consideration of friability and uninterrupted rolling of tablets in subsequent EC coating process, the hardness was set at a range of 80–100 N.

Effect of Ratio of Pore-Former and Coating Weight Gain

To study the effect of pore-former in coating solution, drug release from the tablets coated with different ratios of Surelease® and Opadry® was evaluated in a similar manner. Figure 5 a and b separately show the release profiles of HPMC K4M and K100LV-based matrices coated with various Surelease®:Opadry® ratios (80:20, 60:40, *w/w*). The weight gains of tablets were all about 3.5 ± 0.3%.

The results showed that when proportion of pore-former was 20%, there was an initial lag time ranged about 0.5–1 h in the release profiles, followed by linear release. As the ratio of Surelease®:Opadry® decreased, the lag time was gradually eliminated. However, the release rate decreased in the final period. The effect of the coating film on drug release weakened.

When porogenic agent contacted with media, it dissolved to form channels that allow the entrance of water. The HPMC matrix underwent hydration and swelled to form a gel. And then, coating film ruptured on tablet edges. Therefore, the lag time might represent the time that the media penetrated into the matrix and dissolved the drug (15,29). The increased concentration of pore-former could shorten the time of media uptake and consequently speed up the drug release. Nevertheless, it was worth noting that when the proportion of Opadry® was too high, the film was easily broken or flaked after being contacted with the media, eventually leading to uncontrollable drug release.

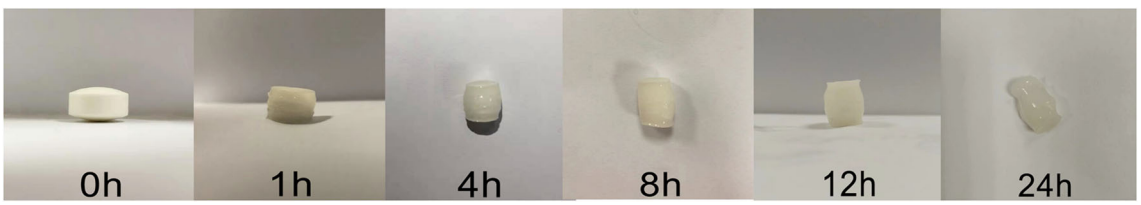

Fig. 3. Images of AH coated tablets (Surelease®:Opadry®, 80:20, 5.5 ± 0.3% WG, *w/w*) in dissolution media along with time

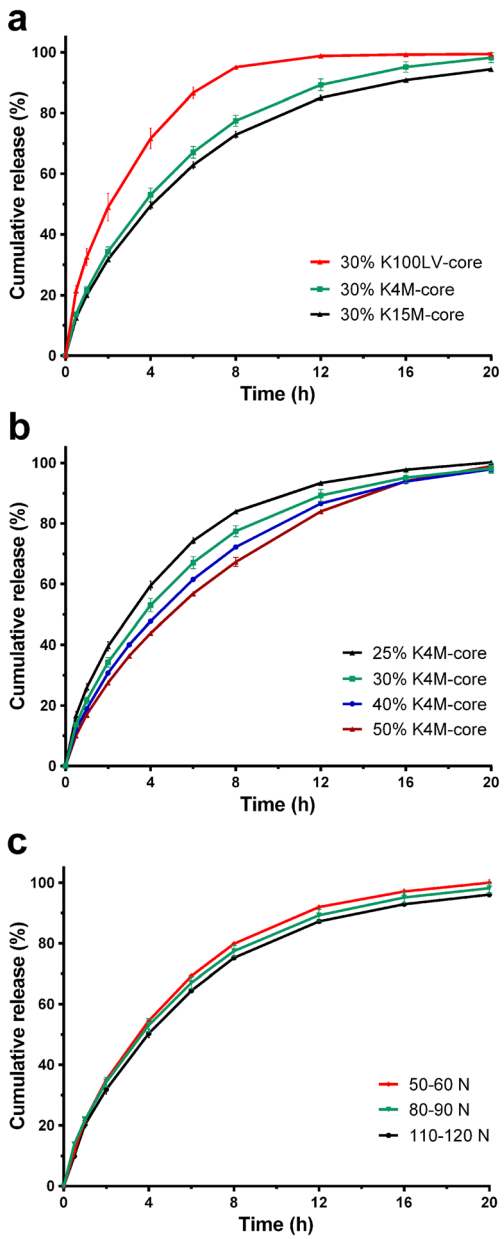

Fig. 4. Drug release profiles of uncoated AH matrix tablets with different **a** viscosity grade and **b** amounts ofHMPC and **c** hardness (HPMC K4M-based) (mean ± SD, $n = 3$)

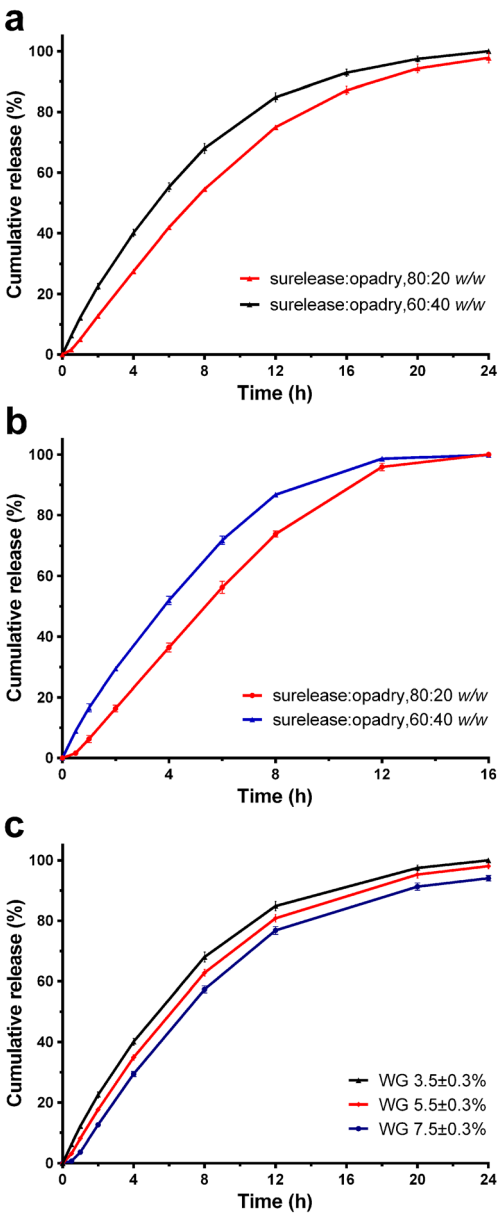

Fig. 5. Drug release on **a** HPMC K4M-based and **b** HPMC K100LV-based matrices coated with different Surelease®:Opadry® ratios and **c** HPMC K4M-based matrices (Surelease®:Opadry®, 60:40, *w/w*) with different weight gains (mean ± SD, $n = 3$)

Drug release profiles from HPMC K4M-based matrices (Surelease®:Opadry®, 60:40, *w/w*) with different weight gains are shown in Fig. 5c. Similarly, the lag time could be adjusted by the coating loads. At low coating weight gains, the phenomenon of time lag was less obvious. In order to form films that completely wrapped on the surface of the core tablets, the weight gain should be no less than 3.0%.

The HPMC K4M-based AH-coated tablets (Surelease®:Opadry®, 80:20, 3.5 ± 0.3% WG, *w/w*) were placed at 60°C, 75% ± 5% RH, 4500 lx ± 500 lx conditions without seal for 10 days, respectively. There was no obvious appearance change of tablets and no significant reduction in drug content. In addition, no significant change in release rate was observed. (Data not shown. The stability at accelerated and long-term storage condition is in progress).

Table V. The Kinetic Parameters of Core Tablets with Different Grades of HPMC

Formulations	k	n	R^2
HPMC K100LV-based core tablets	35.40	0.54	0.9995
HPMC K4M-based core tablets	21.54	0.61	0.9985
HPMC K15M-based coated tablets	20.65	0.57	0.9910

Table VI. The Kinetic Parameters of Coated Tablets with Different Pore-Former Ratios and Coating Weight Gains

Formulations	k	R^2
HPMC K4M-based coated tablets (80:20, 3.5 ± 0.3%,WG, *w/w*)	6.2844	0.9912
HPMC K4M-based coated tablets (60:40, 3.5 ± 0.3%,WG, *w/w*)	7.7028	0.9895
HPMC K100LV-based coated tablets (80:20, 3.5 ± 0.3%, WG, *w/w*)	9.424	0.9979
HPMC K100LV-based coated tablets (60:40, 3.5 ± 0.3%, WG, *w/w*)	11.044	0.9971
HPMC K100LV-based coated tablets (60:40, 7.5 ± 0.3%, WG, *w/w*)	7.3927	0.9912

Drug Release Mechanism for Uncoated and Coated AH Matrix Tablets

In vitro drug release kinetics was simulated using equations shown as follows of zero-order model and Power Law equation:

$$\text{Zero-order}: M_t/M_\infty = kt$$
$$\text{Power Law}: M_t/M_\infty = kt^n$$

M_t/M_∞ is the fraction of drug released at time t, k refers to the kinetic constant, and n is the diffusional exponent for drug release. The dissolution data up to ~80% was used for analysis. The drug release data of uncoated tablets was fitted to Power Law equation (Table V), and the drug release data of coated tablets was fitted to zero-order model (Table VI). For cylindrical matrix tablets, if $0.46 < n < 0.89$, the mechanism is non-Fickian release (anomalous transport) (4,30–33). For core tablets, n values were in the range of 0.54–0.61 (correlation coefficient, $R^2 > 0.99$), indicating that the release was mainly controlled by diffusion and HPMC swelling (non-Fickian kinetics). The viscosity of HPMC had little effect on release kinetics. However, k values were inversely proportional to HPMC viscosity. For coated tablets, the R^2 of linear fitting were greater than 0.99, except the formulation of HPMC K4M-based coated tablets (60:40, 3.5 ± 0.3%, WG, *w/w*) (but very close to). At a higher pore-former ratio, the coating membrane was with more porous and cracked faster, resulting in an increase in drug release. Besides, addition of the coating weight gains could slow down the release rate. The results indicated that application of the Surelease®:Opadry® coating could lead to zero-order release kinetics.

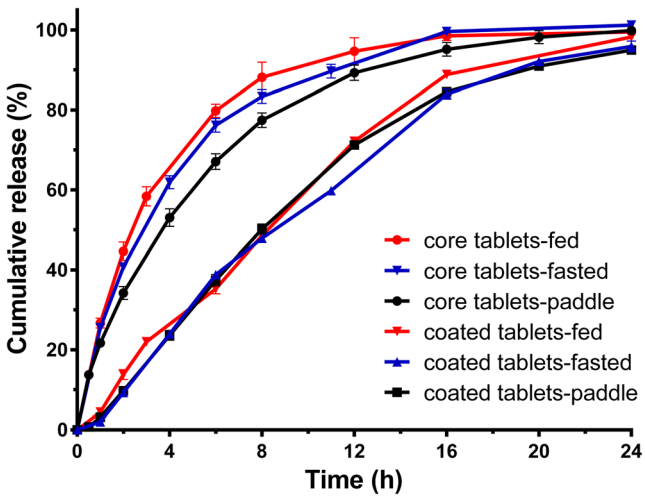

Fig. 6. Drug release profiles of uncoated and coated AH matrix tablets from the USP Apparatus III. (mean ± SD, $n = 3$)

Drug Release Measured by Using USP Apparatus III

The drug release from uncoated and coated AH matrix tablets (30% HPMC, Surelease®:Opadry®, 80:20, 3.5 ± 0.3% WG, *w/w*) was measured by reciprocating cylinder method (Fig. 6). The passage through the gastrointestinal tract was simulated using a pH gradient to test whether varying pH conditions had influence on drug release. Fasted- and fed-state conditions were varied from different pH gradients and corresponding residence time at each site. As shown in Fig. 8, dissolution tests of core tablets performed with USP apparatus III were different from that performed with the paddle apparatus. In comparison, release profiles of coated tables

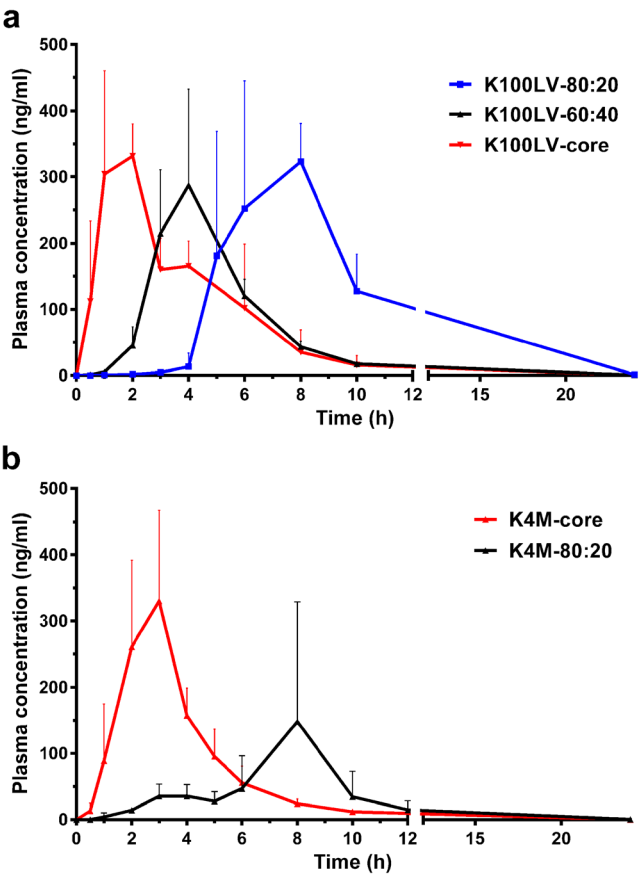

Fig. 7. Mean plasma concentration-time profiles of **a** HPMC K100LV-based AH tablets and **b** HPMC K4M-based AH tablets (mean ± SD, $n = 3$)

Table VII. Pharmacokinetic Parameters of AH Tablets after Oral Administration in Beagle Dogs

Parameters	K4M-based core tablets	K4M-based coated tablets (80:20)	K100LV-based core tablets	K100LV-based coated tablets (80:20)	K100LV-based coated tablets (60:40)
T_{max}(h)	2.67 ± 0.58	8.00 ± 1.06	1.67 ± 0.58	7.33 ± 1.15	4.67 ± 1.15
C_{max}(μg/L)	403.73 ± 167.18	153.32 ± 194.27	385.70 ± 120.06	438.77 ± 149.83	310.73 ± 155.87
$t_{1/2}$ (h)	2.64 ± 0.33	2.42 ± 1.00	2.12 ± 1.00	1.98 ± 0.08	2.40 ± 0.96
AUC_{0-t}[(μg/L) h]	1146.36 ± 198.82	655.17 ± 651.14	1426.00 ± 609.94	2252.09 ± 712.65	1168.48 ± 268.64
MRT (h)	4.12 ± 0.84	7.14 ± 2.05	3.78 ± 0.61	8.49 ± 0.97	5.37 ± 0.57

were nearly superimposable and lag time also existed both in fasted- or fed-state conditions. Apparently, tablet release did not exhibit pH dependence in the gastrointestinal pH range. In the fasted state, gastric volumes are generally less than 250 mL (34). Paddle method usually use media volume in the range of 500–1000 mL, which is less physiologically relevant. While the reciprocating cylinder method adopts a volume of up to 250 mL per vessel. Besides, it has no hydrodynamic dead zone, which is different from the hydrodynamic pattern of the paddle method (35). The release of coated tablets was hardly affected by these condition changes. Overall, the results indicated that the application of coating films could reduce drug release variability remarkably.

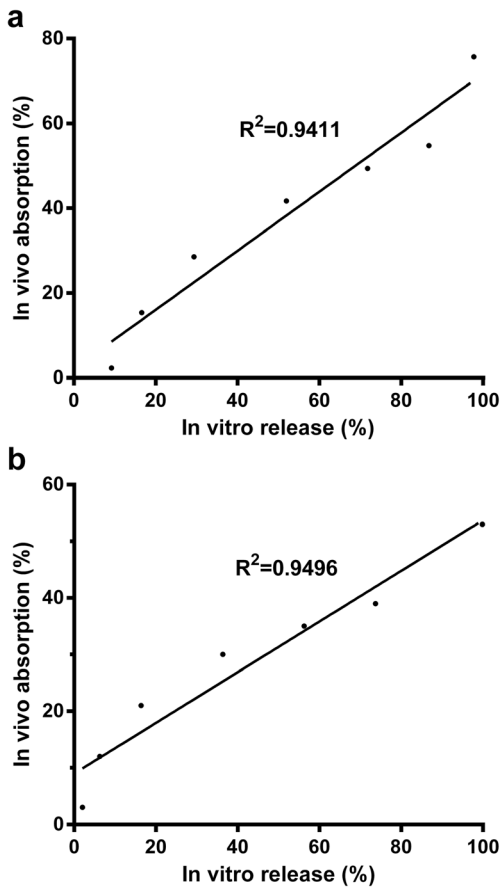

Fig. 8. *In vivo/in vitro* correlation of **a** HPMC K100LV-based coated tablets (Surelease®:Opadry®, 80:20, 3.5 ± 0.3% WG, *w/w*) and **b** HPMC K100LV-based coated tablets (Surelease®:Opadry®, 60:40, 3.5 ± 0.3% WG, *w/w*)

In Vivo Pharmacokinetic Study in Beagle Dogs

Pharmacokinetic experiments of different formulations (30% HPMC, 3.5 ± 0.3% WG, *w/w*) were performed in beagle dogs to evaluate the *in vivo* absorption behavior. The mean plasma concentration-time curves and the major pharmacokinetic parameters of self-made uncoated and coated AH tablets are presented in Fig. 7 and Table VII, respectively. From Fig. 7a, it can be found that the absorption of HPMC K100LV-based AH core tablets was, as expected, fast after oral administration. In contrast, the absorption of AH-coated tablets was delayed. The lag time became longer as the permeability of coating membrane decreased, which was consistent with the *in vitro* drug release trend. The similar result can also be derived from Fig. 7b. However, the AUC0-t of K4M-based coated tablets (Surelease®:Opadry®, 80:20, 3.5 ± 0.3% WG, *w/w*) was far less than the AUC0-t of core tablets. The possible reason might be that the gastrointestinal emptying time of beagle dogs is only about 6 h (36), and the coated tablets were excreted before complete release. As the formulations changed, the overall trend of drug release *in vitro* and *in vivo* was consistent. *In vivo* absorption fraction (Fa) was calculated through convolution/deconvolution methods by DAS 3.2.2 software. The cumulative release *in vitro* (Ft) was selected as the independent variable and Fa as the dependent variable. The linear regression equation for HPMC K100LV-based coated tablets (Surelease®:Opadry®, 80:20, 3.5 ± 0.3% WG, *w/w*) was $y = 0.4476x + 8.9733$ ($R^2 = 0.9411$) and equation for HPMC K100LV-based coated tablets (Surelease®:Opadry®, 60:40, 3.5 ± 0.3% WG, *w/w*) was $y = 0.6963x + 2.1272$ ($R = 0.9496$). They suggested that good correlation existed between the *in vitro* drug release and *in vivo* drug absorption (Fig. 8). Though the sample size should be expanded and pharmacokinetic experiments needed to be further optimized, these results could provide useful guidance on future development.

CONCLUSION

AH membrane-coated matrix tablets were successfully prepared and evaluated in this study. Different release rates could be obtained by adjusting the viscosity and amount of HPMC, percentage of pore-former in coating dispersions, and membrane weight gain. The latter two factors were significant for acquiring zero-order release kinetics. The pharmacokinetic study of different formulations showed that lag time became longer as the permeability of coating membrane decreased, which was consistent with the *in vitro* drug release trend. The results indicated the possibility of tailoring the release profile of a water-soluble drug from directly compressed HPMC matrices as the polymeric core by applying EC film coating with

appropriate levels of pore-former and membrane weight gains. Combination of matrix and barrier-membrane coating was feasible for further application in industrialization and commercialization, not only for high soluble drugs.

REFERENCES

1. Rane M, Parmar J, Rajabi-Siahboomi A. Hydrophilic matrices for oral extended release: influence of fillers on drug release from HPMC matrices. Pharma Times. 2010;42(4):41–5.
2. Colombo P. Swelling-controlled release in hydrogel matrices for oral route. Adv Drug Deliv Rev. 1993;11(1):37–57.
3. Timmins P, Pygall S, Melia C. Hydrophilic matrix tablets for oral controlled release. AAPS advances in pharmaceutical sciences series. New York: Springer; 2014. p. 18–72.
4. Asare-Addo K, Levina M, Rajabi-Siahboomi AR, Nokhodchi A. Study of dissolution hydrodynamic conditions versus drug release from hypromellose matrices: the influence of agitation sequence. Colloids Surf B: Biointerfaces. 2010;81(2):452–60.
5. Rowe RC, Sheskey PJ, Cook WG, Fenton ME. Hand book of pharmaceutical excipients. 7th ed. London: The Pharmaceutical Press; 2012.
6. Using METHOCELTM cellulose ethers for controlled release of drugs in hydrophilic matrix systems. http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_0379/0901b803803797ad.pdf?filepath=methocel/pdfs/noreg/19802075.pdf&fromPage=GetDoc. Accessed 2 Dec 2013.
7. Weitschies W, Wedemeyer R-S, Kosch O, Fach K, Nagel S, Söderlind E, et al. Impact of the intragastric location of extended release tablets on food interactions. J Control Release. 2005;108(2):375–85.
8. Huang X, Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J Control Release. 2001;73(2):121–36.
9. Salar-Behzadi S, Toegel S, Viernstein H. Innovations in coating technology. Recent Pat Drug Deliv Formul. 2008;2:209–30.
10. Dekyndt B, Verin J, Neut C, Siepmann F, Siepmann J. How to easily provide zero order release of freely soluble drugs from coated pellets. Int J Pharm. 2015;478(1):31–8.
11. Siepmann J, Siepmann F. Stability of aqueous polymeric controlled release film coatings. Int J Pharm. 2013;457(2):437–45.
12. Ahmed A, Souad S. Effect of viscosity grades of ethylcellulose on the sustained release properties of indomethacin from its tablets matrix. Afr J Pharm Pharmacol. 2008;2:153–6.
13. Murtaza G. Ethylcellulose microparticles: a review. Acta Pol Pharm. 2012;69:11–22.
14. Marucci M, Andersson H, Hjärtstam J, Stevenson G, Baderstedt J, Stading M, et al. Newinsights on how to adjust the release profile from coated pellets by varying the molecular weight of ethyl cellulose in the coating film. Int J Pharm. 2013;458(1):218–23.
15. Linda AF. Aqueous polymeric coatings for pharmaceutical dosage forms. 4th Ed. Drugs and the Pharmaceutical Sciences. Boca Raton: CRC Press; 2016. p. 301-4.
16. Felton LA, Porter SC. An update on pharmaceutical film coating for drug delivery. Expert Opin Drug Deliv. 2013;10(4):421–35.
17. Mohamed FA, Roberts M, Seton L, Ford JL, Levina M, Rajabi-Siahboomi AR. Film-coated matrix mini-tablets for the extended release of a water-soluble drug. Drug Dev Ind Pharm. 2015;41(4):623–30.
18. Emeje M, Kunle O, Ofoefule S. Compaction characteristics of ethylcellulose in the presence of some channeling agents: technical note. AAPS PharmSciTech. 2006;7(3):581–4.
19. Cheng L, Gai X, Wen H, Liu D, Tang X, Wang Y, et al. Aqueous polymer dispersion coating used for osmotic pump tablets: membrane property investigation and IVIVC evaluation. AAPS PharmSciTech. 2017;19(1):242–50.
20. Lecomte F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. Polymer blends used for the coating of multiparticulates: comparison of aqueous and organic coating techniques. Pharm Res. 2004;21(5):882–90.
21. Mehta RY, Missaghi S, Tiwari SB, Rajabi-Siahboomi AR. Application of ethylcellulose coating to hydrophilic matrices: a strategy to modulate drug release profile and reduce drug release variability. AAPS PharmSciTech. 2014;15(5):1049–59.
22. Klein S, Seeger N, Mehta R, Missaghi S, Grybos R, Rajabi-Siahboomi A. Robustness of barrier membrane coated metoprolol tartrate matrix tablets: drug release evaluation under physiologically relevant in vitro conditions. Int J Pharm. 2018;543(1):368–75.
23. Klein S. Predicting food effects on drug release from extended-release oral dosage forms containing a narrow therapeutic index drug. Dissolut Technol. 2009;16:28–38.
24. Asare-Addo K, Levina M, Rajabi-Siahboomi AR, Nokhodchi A. Effect of ionic strength and pH of dissolution media on theophylline release from hypromellose matrix tablets - apparatus USP III, simulated fasted and fed conditions. Carbohydr Polym. 2011;86(1):85–93.
25. Papadimitriou E, Buckton G, Efentakis M. Probing the mechanisms of swelling of hydroxypropylmethylcellulose matrices. Int J Pharm. 1993;98(1):57–62.
26. Rahman M, et al. Evaluation of various grades of hydroxypropylmethylcellulose matrix systems as oral sustained release drug delivery systems. J Pharm Sci Res. 2011;3(1):930–8.
27. Nokhodchi A, Asare-Addo K. Drug release from matrix tablets: physiological parameters and the effect of food. Expert Opin Drug Deliv. 2014;11(9):1401–18.
28. Kavanagh N, Corrigan OI. Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition. Int J Pharm. 2004;279(1):141–52.
29. Munday DL, Fassihi AR. Controlled release delivery: effect of coating composition on release characteristics of mini-tablets. Int J Pharm. 1989;52(2):109–14.
30. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2012;64:163–74.
31. Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int J Pharm. 1989;57(2):169–72.
32. Zhang C, Tang J, Liu D, Li X, Cheng L, Tang X. Design and evaluation of an innovative floating and bioadhesive multiparticulate drug delivery system based on hollow structure. Int J Pharm. 2016;503(1):41–55.
33. Wang L, Chen K, Wen H, Ouyang D, Li X, Gao Y, et al. Design and evaluation of hydrophilic matrix system containing polyethylene oxides for the zero-order controlled delivery of water-insoluble drugs. AAPS PharmSciTech. 2016;18(1):82–92.
34. Schiller C, Fröhlich CP, Giessmann T, Siegmund W, Mönnikes H, Hosten N, et al. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment Pharma Ther. 2005;22:971–9.
35. Kostewicz ES, Abrahamsson B, Brewster M, Brouwers J, Butler J, Carlert S, et al. In vitro models for the prediction of in vivo performance of oral dosage forms. Eur J Pharm Sci. 2014;57:342–66.
36. Sjögren E, Abrahamsson B, Augustijns P, Becker D, Bolger MB, Brewster M, et al. In vivo methods for drug absorption - comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects. Eur J Pharm Sci. 2014;57:99–151.